Author’s response to reviews

Title: Impact of an integrated care program on glycemic control and cardiovascular risk factors in patients with type 2 diabetes in Saudi Arabia: An interventional parallel-group controlled study

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Point by point response for the reviewers

Response to Reviewer 1 (Angeliki Angelidi):

Could the authors propose any potential contributing factors or underlying causes for BMI increase observed in the intervention group?
This could be explained by the consistently higher doses and multiple insulin types used in the intervention group compared with the control (97.4% versus 63.2%, p<0.001), more mixed insulin types (91.3% versus 33.8%, p<0.001), more insulin with multiple daily doses (p<0.001), are known to be associated with weight gain. One study found that weight gain was not due to an increase in food intake when administering insulin. However, the patients’ bodies may increase the efficiency in using glucose and other fuels when the glycemic control improves.[1] Also, in the intervention group had more poor glycemic control HbA1c (11.2 ± 1.4 [99 mmol/mol (84–114)] versus 10.1 ± 1.6 (87 mmol/mol [69–104]), p<0.001) compared with the control group which more comes with the nature of disease and progression of insulin resistance that cause weight gain. However, weight gain due to insulin used can be overcome if increased the physical activity with regular exercise to prevent insulin-induced weight gain, but the insulin doses will need to be adjusted downward to prevent low blood sugars.[2] The type of insulin patient use and the doses are both important to consider in the overall management of diabetes and the body weight, in overweight type 2 diabetic subjects. The use of once-daily Levemir (detemir) caused less weight gain and less frequent hypoglycemia than use of NPH even combined with use of rapid-acting injections of a separate insulin for meals (and the same is likely true when using Lantus, or insulin glargine). Using a basal insulin alone (once or twice daily) or following a basal-bolus regimen can benefit by making sure that insulin doses are regulated effectively to prevent blood sugar lows and highs — while using as little insulin as absolutely necessary to get the desired glycemic effect.[3]

According to the authors: "intensified insulin treatment in a primary care setting was associated with marked improvement in glycemic control, modest improvements in blood lipids, and a slight non-significant improvement in BP" as well as

"However, the intervention group experienced a statistically significant increase in body weight (3.7%, 95% CI = 2.9%, 4.5%)". Taking the above into consideration, how one could suggest the ulterior cardiovascular protective role and the cost-effective role of the program?

In the UK Prospective Diabetes Study (UKPDS), untreated patients with T2DM lost about 4% of their beta-cell function per year. Given the fact that T2DM is a disease of progressive beta-cell decline, most patients will eventually require insulin therapy to control their disease and the study showed that (97.4% versus 63.2%) in the intervention group compared with control group.[4] Assemble result was observed in UKPDS, which showed that Across all therapies (i.e., sulfonylurea, insulin) patients in the intensive-treatment group gained, on average, 3.1 kg more than patients in the conventional-treatment group. In addition, in the subset of patients treated with insulin therapy, patients in the intensive-treatment group (more insulin used) gained an average of 4.0 kg compared with patients in the conventional-treatment group. In our study the increase in body weight due to insulin. Furthermore, in UKPDs showed that the difference in glycated hemoglobin (A1C) levels between the intensive-treatment group and the conventional-treatment group was only 0.9%. This suggests that an A1C drop of 1% may translate into a 4-kg weight gain over time.[5] This gains importance from the evidence that minor reductions in HbA1c are associated with major reductions in cardiovascular complications and mortality among patients with T2D. Thus, a 1% reduction of HbA1c is associated with a 37% reduction in microvascular complications, 14% reduction in myocardial infarction, and a 21% reduction in diabetes-related mortality.[6] Moreover, this program reduce the overall cost, because the
glycemic control by implementing the integrated care program reduce the cost of diabetes complication. International Diabetes Foundation in 2013 estimated that diabetes cost to individuals and societies will increase over the next 2 decades by about 55% worldwide, with a special increase by 96% in the Middle East region.[7] Alhowaish et al., estimated that Saudi healthcare system diabetes expenses increased by five-folds during the last 2 decades, which represented one dollar for each 11 spent dollars. Therefore, the expected substantial increase in the size of diabetes population in Saudi Arabia together with the persistence of its risk factors such as obesity, sedentary life style, and smoking will probably be translated into a huge surge in the healthcare utilization and allocated costs in the next 2 decades.[8]

Was smoking cessation as well as exercise programs included in the intensive intervention group?

The integrated care program included dietitian and health educator that worked collaboratively for diabetic patients. The health educator worked to modify behavior and self-manage the disease and its related condition such as healthy eating, smoking cessation, increase physical activity and type of exercise coupled with patient disease status, monitoring, improve the adherence to medications and design a plan for exercise intervention program. While dietitian worked more to improve patient diet to control patient's blood sugar, lipid profile and blood pressure.

In addition, during patient's visits to multidisciplinary team. The patient was referred to smoking cessation clinic if the patient was a smoker. Frequent follow up were carried out during continuing follow up.

Could diabetes duration and to be included in Table 1?

Diabetes duration is now included for the two groups with a two-sample independent t-test in Table 1.

How could the authors explain the baseline differences between the two groups? Could selection bias be excluded?

There is differences between the two groups at enrollment. However, these differences were not in one direction, were less clinically meaningful, and probably had no effect on the study findings. For example, the patients in the control group, who had slightly more comorbidities, had slightly better glycemic control. Moreover, the differences in hypertension and dyslipidemia were not associated with differences in BP or blood lipids. The lack of blindness for care providers may contribute to bias in the results. We tried to minimize such effects by blinding the results to the outcomes assessors (i.e., labs workers and nurses).

Did the authors evaluate the type of personality of the participants between the two groups?

Poor control of diabetes and the use of insulin both significantly increase the risk of psychological symptoms. During the patient-physician visit, the Patient health Questionnaire PH9 was considered diagnostic tool for mental health disorder for depression, while the GAD-7 was used as brief scale for anxiety.[9]
Response to Reviewer 2 (Janet Hanley):

Janet Hanley, PhD (Reviewer 2): This paper reports a single centre RCT of a management programme for people with type 2 diabetes in Saudi Arabia. It is reported to CONSORT standards. The results showed that the programme was successful in improving diabetes control with the associated variables suggesting that the mechanism was increased clinic visits leading to escalation of insulin therapy. The weight gain amongst the intervention group is consistent with this mechanism.

The study is not particularly novel and the finding that intensive treatment leads to improved control is consistent with the literature. What is novel is the setting and the very poor level of diabetes control of the participants. The authors point out the particular problems with diabetes in Saudi Arabia and it may be worth including the name of the country in the title.

The title was changed in the manuscript as requested.

The main weakness of the study is the difference between the intervention and control groups. This is mentioned but the choice to present unadjusted statistics should also be justified.

There is differences between the two groups at enrollment. However, these differences were not in one direction, were less clinically meaningful, and probably had no effect on the study findings. For example, the patients in the control group, who had slightly more comorbidities, had slightly better glycemic control. Moreover, the differences in hypertension and dyslipidemia were not associated with differences in BP or blood lipids. In Table 4 a multivariate analysis, using multiple linear regression was employed using the variables that may influence HbA1c control. The variables considered age, sex, intervention vs. control, number of clinical visits, number of comorbidities, diabetes duration, insulin and oral medications, and insulin dose.

The other weakness of this study is the lack of a health economic evaluation of the intervention, and this should be addressed in the discussion.

The lack of health economic evaluation is now addressed in the study’s limitations.

Bibliography


3. Montañana CF, Herrero CH, Fernandez MR. Less weight gain and hypoglycaemia with once-daily insulin detemir than NPH insulin in intensification of insulin therapy in


